

Amendments To The Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

1-2 (Canceled)

3. (Currently amended) [[The method according to claims 1 or 2,]] A method for controlling the flux of penetrants across an adaptable semi-permeable porous barrier comprising the steps of:

preparing a formulation by suspending or dispersing said penetrants in a polar liquid in the form of fluid droplets surrounded by a membrane-like coating of one or several layers, said coating comprising at least two kinds or forms of amphiphilic substances with a tendency to aggregate;

wherein said at least two substances differ by at least a factor of 10 in solubility in said polar liquid;

wherein said penetrants are able to transport agents through the pores of said barrier or enable agent permeation through the pores of said barrier after penetrants have entered the pores;

selecting a dose amount of said penetrants to be applied on a predetermined area of said barrier to control the flux of said penetrants across said barrier;

applying the selected dose amount of said formulation containing said penetrants onto said area of said porous barrier; and

[[characterized in that]] wherein the pH of the formulation is between 3 and 10 [[,more preferably between 4 and 9, and most preferably between 5 and 8]].

4. (Currently amended) The method according to claim 3, wherein [[any one of the preceding claims, characterized in that]] the formulation further comprises:

- at least one thickening agent in an amount that increases the formulation viscosity to maximally 5 Nm/s[[, more preferably up to 1 Nm/s, and most preferably up to 0.2Nm/s,]] so that formulation spreading-over, and drug retention at the application area is enabled,

- and/or at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100% per 6 months[[, more preferably to less than 100% per 12 months and most preferably to less than 50% per 12 months]]
- and/or at least one microbiocide in an amount that reduces the bacterial count of 1 million germs added per g of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of enterobacteria, and to less than 1 in the case of *Pseudomonas aeruginosa* or *Staphylococcus aureus*, after a period of 4 days.

5. (Canceled)

6. (Currently amended) The method of claim [[1]] 3 wherein said substances when in the form of homo-aggregates (for the more soluble substance) or of hetero-aggregates (for any combination of both said substances) have a preferred average diameter smaller than the diameter of homo-aggregates containing merely the less soluble substance.

7. (Currently amended) The method of claim [[1]] 3 wherein the more soluble substance tends to solubilise the droplet and the content of such substance is to up to 99 mol-% of solubilising concentration or else corresponds to up to 99 mol-% of the saturating concentration in the unsolubilised droplet.

8. (Currently amended) The method of claim [[1]] 3 wherein the presence of the more soluble substance lowers the average elastic energy of the membrane-like coating to a value at least 5 times lower than the average elastic energy of red blood cells or of phospholipid bilayers with fluid aliphatic chains.

9-34 (Canceled)

35. (Currently amended) A patch comprising a formulation [[of claim 1 in an amount corresponding to the desired dose per area]] prepared by suspending or dispersing penetrants in a polar liquid in the form of fluid droplets surrounded by a

membrane-like coating of one or several layers, said coating comprising at least two kinds or forms of amphiphilic substances with a tendency to aggregate, wherein said at least two substances differ by at least a factor of 10 in solubility in said polar liquid, wherein said penetrants are able to transport agents through the pores of an adaptable semi-permeable porous barrier or enable agent permeation through the pores of said barrier after penetrants have entered the pores, wherein the pH of the formulation is between 3 and 10 and wherein the formulation is present in an amount corresponding to a desired dose per area.

36. (Currently amended) The patch according to [[any one of claims 32 to 35]] claim 35, [[characterized in that the non-occlusive backing liner comprises a polyurethane membrane, preferably a polyester track-etched porous membrane, more preferably a polycarbonate track-etched porous membrane, more preferably a polycarbonate track-etched porous membrane and most preferably a polyethylene microporous membrane]] comprising a non-occlusive backing liner and an inner liner, wherein the backing liner and the inner liner define a reservoir; and/or a matrix layer.

37. (Currently amended) The patch according to [[any one of claims 32 to 36]] claim 36, [[characterized in that]] wherein the inner liner prevents unwanted release of the formulation from the patch during storage and enables rapid skin wetting when contacted with the skin.

38. (Currently presented) The patch according to claim 36 wherein the non-occlusive backing liner exhibits a mean vapor transmission rate (MVTR) of more than 1000 g/m²day.

39. (Currently amended) The patch according to claim [[38]] 36 wherein the penetrant flux across the barrier is controlled by the solvent disappearance across the non-occlusive backing liner.

40. (Currently amended) The patch of claim ~~[[35]]~~ 36 wherein the non-occlusive backing liner has pores of smaller than 100 nm~~[[, preferably smaller than 70 nm and most preferably of smaller than 30 nm]]~~.

41. (Currently amended) The patch of claim ~~[[35]]~~ 36 wherein the non-occlusive backing liner comprises a membrane selected from the group comprising a polyurethane membrane, a polyester track-etched porous membrane, a polycarbonate track-etched porous membrane and a polyethylene microporous membrane.

42-59 (Canceled)

60. (Currently amended) A kit comprising a formulation ~~[[of claim 1]]~~ prepared by suspending or dispersing penetrants in a polar liquid in the form of fluid droplets surrounded by a membrane-like coating of one or several layers, said coating comprising at least two kinds or forms of amphiphilic substances with a tendency to aggregate, wherein said at least two substances differ by at least a factor of 10 in solubility in said polar liquid, wherein said penetrants are able to transport agents through the pores of an adaptable semi-permeable porous barrier or enable agent permeation through the pores of said barrier after penetrants have entered the pores, wherein the pH of the formulation is between 3 and 10 and wherein the formulation is present in an amount which enables the formulation to be applied at ~~[[the]]~~ a selected dose per area.

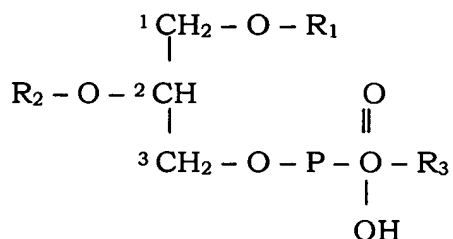
61. (Currently amended) The method according to claim ~~[[54]]~~ 4, ~~[[characterized in that]]~~, wherein said antioxidant is selected from synthetic phenolic antioxidants, such as butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX, etc.), tertiary butylhydroquinone (TBHQ), propyl gallate (PG), 1-O-hexyl-2,3,5-trimethylhydroquinone (HTHQ); aromatic amines (such as diphenylamine, p-alkylthio-o-anisidine, ethylenediamine derivatives, carbazol, tetrahydroindenoindol); phenols and phenolic acids (such as guaiacol, hydroquinone, vanillin, gallic acids and their esters, protocatechuic acid, quinic acid, syringic acid,

ellagic acid, salicylic acid, nordihydroguaiaretic acid (NDGA), eugenol); tocopherols (including tocopherols (alpha, beta, gamma, delta) and their derivatives, such as tocopheryl-acylate (e.g. -acetate, -laurate, myristate, -palmitate, -oleate, -linoleate, etc., or any other suitable tocopheryl-lipoate), tocopheryl-POE-succinate; trolox and corresponding amide- and thiocarboxamide analogues; ascorbic acid and its salts, isoascorbate, (2 or 3 or 6)-o-alkylascorbic acids, ascorbyl esters (e.g. 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or linoleoyl-L-ascorbic acid, etc.); non-steroidal anti-inflammatory agents (NSAIDs), such as indomethacin, diclofenac, mefenamic acid, flufenarnic acid, phenylbutazone, oxyphenbutazone acetylsalicylic acid, naproxen, diflunisal, ibuprofen, ketoprofen, piroxicam, penicillamine, penicillamine disulphide, primaquine, quinacrine, chloroquine, hydroxychloroquine, azathioprine, phenobarbital, acetaminophen); aminosalicylic acids and derivatives; methotrexate, probucol, antiarrhythmics (e.g. amiodarone, aprindine, asocainol), ambroxol, tamoxifen, b-hydroxytamoxifen; calcium antagonists (such as nifedipine, nisoldipine, nimodipine, nicardipine, nilvadipine), beta-receptor blockers (e.g. atenolol, propranolol, nebivolol); sodium bisulphite, sodium metabisulphite, thiourea; chelating agents, such as EDTA, GDTA, desferral; endogenous defence systems, such as transferrin, lactoferrin, ferritin, ceruloplasmin, haptoglobin, haemopexin, albumin, glucose, ubiquinol-10; enzymatic antioxidants, such as superoxide dismutase and metal complexes with a similar activity, including catalase, glutathione peroxidase, and less complex molecules, such as beta-carotene, bilirubin, uric acid; flavonoids (e.g. flavones, flavonols, flavonones, flavanones, chalcones, anthocyanins), N-acetylcysteine, mesna, glutathione, thiohistidine derivatives, triazoles; tannins, cinnamic acid, hydroxycinnamic acids and their esters (e.g. coumaric acids and esters, caffeic acid and their esters, ferulic acid, (iso-) chlorogenic acid, sinapic acid); spice extracts (e.g. from clove, cinnamon, sage, rosemary, mace, oregano, allspice, nutmeg); camosic acid, camosol, carsolic acid; rosmarinic acid, rosmarindiphenol, gentisic acid, ferulic acid; oat flour extracts, such as avenanthramide 1 and 2; thioethers, dithioethers, sulphoxides, tetraalkylthiuram disulphides; phytic acid, steroid derivatives (e.g. U74006F); tryptophan metabolites (e.g. 3-hydroxykynurenine, 3-hydroxyanthranilic acid), and organochalcogenides, or else is an oxidation suppressing enzyme.

62-65 (Canceled)

66. (Currently amended) The method according to claim 3,[[65, characterised in that]] wherein the less soluble aggregating substance is a lipid or lipid-like material; and

wherein the lipid or lipid-like material is a lipid or a lipoid from a biological source or a corresponding synthetic lipid or any of its modifications, said lipid preferably belonging to the class of pure phospholipids corresponding to the general formula



where R₁ and R₂ is an aliphatic chain, typically a C₁₀₋₂₀-acyl, or -alkyl or partly unsaturated fatty acid residue, in particular, an oleoyl-, palmitoeloyl-, elaidoyl-, linoleyl-, linolenyl-, linolenoyl-, arachidoyl-, vaccinyl-, lauroyl-, myristoyl-, palmitoyl-, or stearoyl chain; and where R₃ is hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, C₁₋₄-alkyl, C₁₋₅-alkyl substituted with carboxy, C₂₋₅-alkyl substituted with hydroxy, C₂₋₅-alkyl substituted with carboxy and hydroxy, or C₂₋₅-alkyl substituted with carboxy and amino, inositol, sphingosine, or salts of said substances, said lipid comprising also glycerides, isoprenoid lipids, steroids, sterines or sterols, of sulphur- or carbohydrate-containing lipids, or any other bilayer-forming lipids, in particular half-protonated fluid fatty acids, said lipid is selected from the group comprising phosphatidylcholines, phosphatidylethanolamines- , phosphatidylglycerols, phosphatidylinositols, phosphatidic acids, phosphatidylserines, sphingomyelins or other sphingophospholipids, glycosphingolipids (including cerebrosides, ceramidepolyhexosides, sulphatides, sphingoplasmalogens), gangliosides and other glycolipids or synthetic lipids, in particular with corresponding sphingosine

derivatives, or any other glycolipids, whereby two similar or different chains can be ester-groups-linked to the backbone (as in diacyl and dialkenoyl compound) or be attached to the backbone with ether bonds, as in dialkyl-lipids.

67. (Currently amended) The method according to claim 3,[[65, characterised in that]] wherein the more soluble aggregating substance lowers the average elastic energy of the droplet and is a surfactant or else has surfactant-like properties and/or is a form of said lipid or lipid-like material which is comparably soluble as said surfactant or the surfactant-like material; and

wherein the surfactant or surfactant-like material preferably is a nonionic, a zwitterionic, an anionic or a cationic surfactant, especially a fatty-acid or -alcohol, an alkyl-tri/di/methyl-ammonium salt, an alkylsulphate salt, a monovalent salt of cholate, deoxycholate, glycocholate, glycodeoxycholate, taurodeoxycholate, taurocholate, etc., an acyl- or alkanoyl-dimethyl- aminoxide, esp. a dodecyl-dimethyl-aminoxide, an alkyl- or alkanoyl-N-methylglucamide, N-alkyl-N,N-dimethylglycine, 3-(acyldimethylammonio)-alkanesulphonate, N-acyl-sulphobetaine, a polyethylene-glycol-octylphenyl ether, esp. a nonaethylene-glycol-octylph- enyl ether, a polyethylene-acyl ether, esp. a nonaethylen-dodecyl ether, a polyethylene-glycol-isoacyl ether, esp. a octaethylene-glycol-isotridecyl ether, polyethylene-acyl ether, esp. octaethylenedodecyl ether, polyethylene-glycol-sorbitane-acyl ester, such as polyethylenglykol-20-mo- nolaurate (Tween 20) or polyethylenglykol-20-sorbitan-monooleate (Tween 80), a polyhydroxyethylene-acyl ether, esp. polyhydroxyethylene-lauryl, -myristoyl, -cetylstearyl, or -oleoyl ether, as in polyhydroxyethylene-4 or 6 or 8 or 10 or 12, etc., -lauryl ether (as in Brij series), or in the corresponding ester, e.g. of polyhydroxyethylen-8-stearate (Myrij 45), -laurate or -oleate type, or in polyethoxylated castor oil 40, a sorbitane-monoalkylate (e.g. in Arlacel or Span), esp. sorbitane-monolaurate, an acyl- or alkanoyl-N-methylglucamide, esp. in or decanoyl- or dodecanoyl-N-methylglucamide, an alkyl-sulphate (salt), e.g. in lauryl- or oleoyl-sulphate, sodium deoxycholate, sodium glycodeoxycholate, sodium oleate, sodium taurate, a fatty acid salt, such as sodium elaidate, sodium linoleate, sodium laurate, a lysophospholipid, such as n-octadecylene(=oleoyl)-glycerophosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-acyl-, e.g. lauryl or oleoyl-glycero-

phosphatidic acid, -phosphorylglycerol, or phosphorylserine, n-tetradecyl-glycero-phosphatidic acid, -phosphorylglycerol, or -phosphorylserine, a corresponding palmitoeloyl-, elaidoyl-, vaccenyl-lysophospho lipid or a corresponding short-chain phospholipid, or else a surface-active polypeptide.

68. (Currently amended) The method according to claim 3, wherein [[claims 54 to 67, characterised in that]] the average diameter of the penetrant is between 30 nm and 500 nm[[, more preferably between 40 nm and 250 nm, even more preferably between 50 nm and 200 nm and particularly preferably between 60 nm and 150nm]].

69. (Currently amended) The method according to claim 3, wherein [[claims 54 to 68, characterised in that]] the total dry weight of droplets in a formulation is 0.01 weight-% (w-%) to 40 w-% of total formulation mass[[, more preferably between 0.1 w-% and 30 w-%, and most preferably between 0.5 w-% and 20 w-%]].

70-101 (Canceled)

102. (Previously presented) The method according to claim 66 for the treatment of inflammatory disease, dermatosis, kidney or liver failure, adrenal insufficiency, aspiration syndrome, Behcet syndrome, bites and stings, blood disorders, such as cold-haemagglutinin disease, haemolytic anemia, hypereosinophilia, hypoplastic anemia, macroglobulinaemia, trombocytopenic purpura, furthermore, for the management of bone disorders, cerebral oedema, Cogan's syndrome, congenital adrenal hyperplasia, connective tissue disorders, such as lichen, lupus erythematosus, polymyalgia rheumatica, polymyositis and dermatomyositis, epilepsy, eye disorders, such as cataracts, Graves' ophthalmopathy, haemangioma, herpes infections, neuropathies, retinal vasculitis, scleritis, for some gastro-intestinal disorders, such as inflammatory bowel disease, nausea and oesophageal damage, for hypercalcaemia, infections, e.g. of the eye (as in infections mononucleosis), for Kawasaki disease, myasthenia gravis, various pain syndromes, such as postherpetic neuralgia, for polyneuropathies, pancreatitis, in respiratory disorders, such as asthma, for the management of rheumatoid disease and

osteoarthritis, rhinitis, sarcoidosis, skin diseases, such as alopecia, eczema, erythema multiforme, lichen, pemphigus and pemphigoid, psoriasis, pyoderma gangrenosum, urticaria, in case of thyroid and vascular disorders.

103. (New) The method of claim 3, wherein the pH of the formulation is between 4 and 9.

104. (New) The method of claim 3, wherein the pH of the formulation is between 5 and 8.

105. (New) The method of claim 4, wherein the at least one thickening agent is in an amount that increases the formulation viscosity to maximally 1 Nm/s.

106. (New) The method of claim 4, wherein the at least one thickening agent is in an amount that increases the formulation viscosity to maximally 0.2Nm/s.

107. (New) The method of claim 4, wherein the least one antioxidant is in an amount that reduces the increase of oxidation index to less than 100% per 12 months.

108. (New) The method of claim 4, wherein the least one antioxidant is in an amount that reduces the increase of oxidation index to less than 50% per 12 months.

109. (New) The patch of claim 35, wherein the non-occlusive backing liner has pores of smaller than 70 nm.

110. (New) The patch of claim 35, wherein the non-occlusive backing liner has pores of smaller than 30 nm.

111. (New) The method according to claim 3, wherein the average diameter of the penetrant is between 40 nm and 250 nm.

112. (New) The method according to claim 3, wherein the average diameter of the penetrant is between 50 nm and 200 nm.

113. (New) The method according to claim 3, wherein the average diameter of the penetrant is between 60 nm and 150nm.

114. (New) The method according to claim 3, wherein the total dry weight of droplets in a formulation between 0.1 w-% and 30 w-% of total formulation mass.

115. (New) The method according to claim 3, wherein the total dry weight of droplets in a formulation between 0.5 w-% and 20 w-% of total formulation mass.

116. (New) The method according to claim 3, wherein the flux across the barrier is increased by enlarging the applied dose per area of penetrants.

CONCLUSION

Applicant respectfully requests early consideration and allowance of the subject application.

Applicants believe that additional fees are not required in connection with the consideration of the within matter. However, if for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

Respectfully submitted,



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